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PHARMACOKINETICS AND DISPOSITION

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Lamotrigine pharmacokinetic evaluation in epileptic patients submitted to VEEG monitoring

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Abstract *Objective:* The aim of the present study was to evaluate the pharmacokinetic profile of lamotrigine (LTG) in epileptic patients submitted to video-electroencephalography (VEEG) monitoring and, in addition, to investigate the influence of concomitant antiepileptic drugs (AEDs) on the kinetics of LTG. *Methods:* The analysis assumed a one-compartment open model with first-order absorption and elimination. The kinetic estimates obtained in this population were validated by using the Prediction-Error approach. The influence of medication was also assessed by the calculation of the LTG concentration-to-dose ratio. Patients (n=135) were divided into four groups according to the co-medication: Group 1, patients taking LTG with enzyme-inducer agents; Group 2, patients receiving LTG with valproic acid; Group 3, patients receiving both inducers and inhibitors of LTG metabolism; Group 4, patients under AEDs not known to alter LTG metabolism. *Results:* The obtained estimates for clearance (CL) (L/h/kg) [0.075±0.029 (Group 1), 0.014±0.005 (Group 2), 0.025±0.008 (Group 3) and 0.044±0.011 (Group 4)] appear to be the most appropriate set to be implemented in clinical practice as prior information, as demonstrated by the accuracy and precision of the measurements. In addition, the influence of co-medication on the LTG profile was further confirmed by the basal LTG concentration-to-dose ratio. *Conclusion:* The results of the present investigation may contribute to achieving the goal of optimizing patients' clinical outcomes by managing their medication regimen through measured drug concentrations. Patients submitted to VEEG monitoring may benefit from this study, as the results may be used to provide better drug management in this medical setting.

Keywords Antiepileptics · Epilepsy · Interactions · Lamotrigine · Pharmacokinetics · VEEG

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Introduction

The selection of an antiepileptic drug (AED) is guided by the aim of achieving maximum seizure control with minimum side effects. In the search for better approaches to refractory epilepsy, a new generation of AEDs has emerged. Lamotrigine (LTG) is a widely used AED currently available in more than 90 countries. It was introduced as adjunct treatment of partial seizures in Europe in 1991 and in the United States in 1994. It has recently been suggested that LTG may be useful as initial monotherapy in patients with newly diagnosed epilepsy [1–3]. At the present time it has the approval of the U.S. Federal Drug Administration as a monotherapy, following conversion in patients receiving AEDs with enzyme-inducing properties. Furthermore, there is an increasing interest in its properties for treating bipolar disorders [4].

Lamotrigine is metabolized mainly in the liver by glucuronidation and excreted renally as a glucuronide conjugate [5, 6]. The metabolism of LTG is catalysed by UDPGT1A4, an isoenzyme of the uridine 5′-diphosphate-glucuronosyltransferase (UDPGT) family of enzymes [7]. The coadministration of hepatic enzyme-inducing (IND) agents, such as phenytoin (PHT), carbamazepine (CBZ), phenobarbitone (PB) or primidone (PRM), significantly increases the systemic clearance of LTG [8], while valproic acid (VPA), a known inhibitor of glucuronidation, significantly reduces the elimination of LTG [9, 10].

Although polytherapy regimens heighten the risk of side effects and drug interactions, consequently reducing patient compliance and raising therapy costs, the epileptic population often presents complex concurrent therapies. In addition, several characteristics of LTG would suggest that there is a clinical need to individualize patient therapy through the use of therapeutic drug monitoring (TDM) [11–13]. In addition, patients submitted to video-electroencephalography (VEEG) monitoring for diagnostic purposes often agree to AED discontinuation in order to precipitate seizures. A knowledge of the kinetic behaviour of LTG in this subpopulation may contribute to the better management of these patients in that this kinetic information could be used to predict LTG concentrations in this clinical setting.

The aim of the present study was therefore (1) to estimate LTG pharmacokinetic parameters, (2) to validate this estimation by using prediction performance analysis and (3) to further investigate the influence of concomitant AEDs on LTG kinetics by assessing the concentration-to-dose (C/D) ratio.

Materials and methods

Patients

The study was conducted in the VEEG Monitoring Unit of the Neurology Department of Coimbra University Hospital (Portugal). Patients receiving LTG were submitted to VEEG monitoring during a period of 3–11 days for seizure characterization or presurgical evaluation. Routine haematology and blood chemistry assessments were made. The local Ethics Committee of Coimbra University Hospital approved this study, and written informed consent was obtained from all patients.

During the VEEG session, patients agreed to a drug discontinuation protocol in order to precipitate seizures – the methodology adopted in this setting. In the case of polytherapy, the protocol establishes that the first drug to be withdrawn is the concomitant CBZ or VPA. If both drugs are present simultaneously, the withdrawal should start with CBZ.

A total of 652 serum concentrations (peaks and troughs) of 135 Caucasian patients were evaluated. Data were collected from October 1998 to June 2005. Demographic data collected included date of birth, gender, weight, height, medical history and dosage regimens (dose and frequency of dosage), with all details of concomitant medication. The LTG baseline dosage regimen was recorded when the patient arrived at the hospital. The collected data were further matched with individual clinical reports.

Lamotrigine was administered orally, ranging from 25 to 500 mg one to four times daily (Table 1). Patients were included in the study if they their LTG-dose and co-medication had remained unchanged during a period of at least 20 days (fivefold the maximum half-life, which may reach approximately 89 h when associated to VPA).

Blood sampling and assay

Blood samples were collected just prior to the following dose to obtain minimal (or trough) concentrations each morning during the VEEG session. As trough concentrations are insufficient to achieve a complete characterization of the pharmacokinetic profile, two additional sampling time points were established near the t_{max} of lamotrigine. Blood samples were characterized by high-performance liquid chromatography (HPLC), as described elsewhere [14]. Calibration between 0.1 and 15.0 mg/L of LTG concentration provided good accuracy (a mean of 0.013 for the inter-assay), precision (a mean of 6.97% for the inter-assay) and recovery (85%) results. The stability of the samples in this biological fluid at 4° and −25°C has also been reported previously [14]. The serum concentrations of the remaining AEDs (CBZ, VPA, FB, and PHT) were analysed by a fluorescence polarization immunoassay (FPIA) method (Abbott Diagnostics Division, Maidenhead, UK) according to the usual analytical procedures. This approach allowed us to ensure that the patients had taken AEDs regularly.

Pharmacokinetic analysis

The pharmacokinetic (PK) study of plasma LTG concentrations was performed by compartmental analysis, using the non-linear regression computer program WinNonlin® ver. 1.2 (Scientific Consulting, Gaithersburg, Md). The analysis assumed a one-compartment open model with first-order absorption and first-order elimination. This study included 93 patients for the estimation of absorption rate constant (k_a), volume of distribution (V_d) and elimination rate constant (k_e). In the individual estimation, the curve fitting used 4–11 concentrations (peaks and troughs). The general features of patients included in pharmacokinetic study are shown in the Index sample of Table 1. Four treatment groups could be established taking into account the existing patient co-medication: Group 1, LTG and inducer agents; Group 2, LTG and VPA; Group 3, LTG with both inducers and VPA; Group 4, LTG with neither inducer nor inhibitor agents able to alter LTG metabolism, based on present knowledge. In Group 4 only one patient had LTG monotherapy; we were also able to find vigabatrin (VGB; n=1), clobazam (CLB; n=1), topiramate (TPM; n=3) or gabapentin (GBP; n=1). Group 1 patients could be further divided into one-inducer (LTG+CBZ; n=33) and two-inducer (LTG+CBZ+PHT/FB; n=8) subgroups. Three patients were excluded from Group 1 due to a different combination of inducers (LTG+PB/PHT, in a total of 15 samples).

To validate the estimates obtained in the pharmacokinetic study we investigated their predictive capacity in 42 new patients (Validation sample), using one to three concentrations per patient (Table 1). This approach assessed the ability to predict LTG serum concentrations in advance using the PKS programme (PKS® System,

Table 1 Summary of patient characteristics

	Population[a]	
	Index	Validation
Number of patients	90	42
Number of observations per patient	4–11	1–3
Number of concentrations	560	77
Female/male	47/43	27/15
Age (years)[b]	31.4±12.2 (12–64)	29.5±10.9 (12–53)
Weight (kg)[b]	67.4±13.7 (41–105)	67.2±17.6 (36–108)
Height (cm)[b]	164.7±9.7 (148–192)	163.2±9.3 (130–183)
Time interval[b, c] (h)	13.2±2.8 (6.3–24.6)	12.3±3.4 (4.0–24.0)
Co-medication[d] (no of patients)		
Group 1	41	14
Group 2	28	12
Group 3	14	8
Group 4	7	8

[a]Index, Patients included in the pharmacokinetic study; validation, patients included in the prediction performance study
[b]Results expressed as the mean ± standard deviation (range in parenthesis)
[c]Between last intake and blood sampling considering basal levels; only 5% presented the 1 id-scheme (1+0+0) and 1% presented the 4 id-scheme (1+1+1+1)
[d]Group 1, LTG+IND; Group 2, LTG+VPA; Group 3, LTG+VPA+IND; Group 4, LTG+NONE (IND, metabolism inducer; VPA, valproic acid; VPA+IND, valproic acid and inducer; NONE, AEDs not known to modify drug metabolism)

Abbott Diagnostics). The absolute and relative predictive performances were evaluated applying the Prediction-Error analysis, as suggested by Sheiner & Beal [15]. This evaluation involved the calculation of mean prediction error (ME), as a measure of accuracy; mean squared prediction error (MSE), representing precision; the root mean squared prediction error (RMSE), as a measure of both accuracy and precision. In order to perform this study, two sets of the obtained parameters were assembled: P1, which used those parameters obtained with 'All data' results (Table 2) to estimate a priori LTG concentrations; P2, which used the PK parameters obtained in the four treatment groups described above (Table 2). This latter approach evaluates the prediction performance of LTG concentrations using the results obtained in the target population and also investigates the influence of knowledge of co-medication on this prediction. Furthermore, we compared the predictive performance of four different sets of LTG parameters selected from previous published studies (Table 3). The aim of this approach was to assess their ability to predict LTG concentrations and to compare this capacity to that demonstrated by our PK parameter set which demonstrated the best prediction results.

The trough steady-state serum concentrations (mg/L) normalized by daily dose (mg/kg/day) – the C/D ratio – may be used to evaluate the influence of co-medication on LTG treatment [16–19]. Consequently, we decided to pool data (Index and Validation sample) in order to determine the LTG C/D ratio in our patients. This investigation used the first basal LTG concentration level of each patient divided by the respective LTG dose (mg/kg/day) to calculate the basal LTG C/D ratio. We considered basal levels to be each trough concentration measured before the start of drug withdrawal. Using the same criteria for establishing categories described

Table 2 Summary of LTG pharmacokinetic parameters[a] obtained in the study

Parameters[b]	Treatment group[c]				All data
	Group 1	Group 2	Group 3	Group 4	
Number of patients	41	28	14	7	90
Number of concentrations	260	183	79	38	562
k_a (h^{-1})	1.28±1.09	1.67±1.44	1.55±1.06	1.82±1.64	1.49±1.24
V_d/F (L/kg)	1.02±0.29	0.86±0.27	0.90±0.31	1.08±0.34	0.96±0.30
$t_{½}$ (h)	10.5±4.5	42.4±11.2	26.7±10.7	18.2±7.6	23.5±16.2
CL (L/h/kg)	0.075±0.029*	0.014±0.005*	0.025±0.008*	0.044±0.011*	0.046±0.034

*$p \leq 0.001$ (statistical differences were found between all groups)
[a]Results are expressed as the mean ± standard deviation
[b]k_a, absorption rate constant; V_d, volume of distribution; k_e, elimination rate constant; $t_{½}$ time required for 50% elimination
[c]Group 1, LTG+IND; Group 2, LTG+VPA; Group 3, LTG+VPA+IND; Group 4, LTG+NONE (IND, metabolism inducer; VPA, valproic acid; VPA+IND, valproic acid and inducer; NONE, AEDs not known to modify drug metabolism

Table 3 Lamotrigine parameter sets established according to previous published studies

Set number	Parameters[a]				*n*	Reference
	F	k_a (h^{-1})	V_d/F (L/kg)	CL/F (L/h/kg)		
1	0.98[b]	6.16	1.28±0.24[c]	0.049±0.028	22	[8]
2	0.91	1.30	[d]	[e]	527	[21]
3	0.98[b]	3.57	1.12±0.07	0.031±0.011	124	[22]
4	0.98[b]	1.49[f]	1.10±1.00	0.080±0.080	23	[23]

[a]F, Bioavailability fraction; k_a, absorption rate constant; V_d, volume of distribution; CL, clearance
[b]Bibliographical value was used because no F value was reported in the reference study
[c]Mean ± standard deviation
[d]According to author's model, V_d=132 L × 0.735 if female
[e]According to author's model, CL= 40.5+0.428 mL/min × weight × 1.131 if co-medication consists of more than two inducers
[f]Portuguese k_a value was used because no value was available in the reference study

before, four treatment groups were established in accordance with LTG co-medication.

The SPSS® (release 11.5 for Windows, 2002; SPSS, Chicago, Ill.) was used to operate all statistical tests. Parametric statistical calculations were used because the data were normally distributed. The significant probability level chosen was $p \leq 0.05$.

Results

A summary of the pharmacokinetic estimates is shown in Table 2. No statistical difference was found between groups based on a comparison of the V_d/F and k_a estimates. However, the data did exhibit significant differences in clearance (CL) estimates between the four groups established. In Group 1, patients included in the two-inducer subgroup (LTG+CBZ+PHT/FB) presented higher clearance estimates (0.098±0.037 L/h/kg; n=8) than the patients receiving only CBZ (LTG+CBZ) concomitantly with LTG (0.069±0.024 L/h/kg; n=33).

Predictive performance measures are revealed in Tables 4 and 5. The set of parameters nominated as P2 showed a lower ME value (0.05 μg/mL) than P1. The P1 set of parameters showed a slightly negative ME value (−0.98), indicating a minor underprediction (Table 4). P2 also exhibited a lower RMSE value than P1 (1.75 vs. 3.00 μg/mL). The comparison between set P1 and set P2 also revealed significant differences in the accuracy (p<0.05) and the precision (p<0.001) measures. The relative evaluation provided a mean ΔME value of 1.03 [95% confidence interval (CI): 0.40–1.66) and a mean ΔMSE value of 5.97 (95% CI: 2.88–9.05). Accordingly, set P2 seems to be significantly more accurate and precise than P1, indicating that knowledge of the co-medication may contribute to a better prediction of LTG concentrations. In view of this, P2 was chosen as the reference methodology for further evaluation with other sets of PK parameters based on previously published studies (Table 3). The results of this comparative analysis of both accuracy (ME) and precision (MSE) are described in Table 5.

The influence of co-medication on the C/D ratio of the total sample population is presented in Fig. 1. Statistical differences were found between all groups. No difference could be discerned by comparing the kind of inducer included in Group 1 or in Group 3.

Table 4 Predictive performance of LTG concentrations

Sets[a]	Prediction-error[b]	
	ME (μg/mL)	MSE (μg/mL)^2
P1	−0.98	9.01
	(−1.63; −0.32)*	(5.56; 12.47)
P2	0.05	3.05
	(−0.35; 0.45)	(1.76; 4.33)

*Significant differences from zero ($p \leq 0.05$)
[a]P1, Parameter set established in accordance with the estimates ascribed as All data' (Table 2); P2, parameter set established in accordance with the estimates achieved in each treatment group (Table 2)
[b]Values given are the mean (95% CI is given in parenthesis). ME, Mean prediction error; MSE, mean squared prediction error; n=77

Discussion

The results of this pharmacokinetic study involving 90 patients (Index sample) demonstrated a high inter-individual variability in the estimates of the parameters tested; this was particularly true for the elimination rate constant (CV: approx. 70%). Although genetic differences in drug glucuronidation, due to variable expression of the different isoenzymes of UDPGT, may contribute to inter-subject variability in metabolism [20], this high variability between patients is more likely to be attributed to pharmacokinetic interactions.

The sampling time schedule used in this clinical setting allowed us to completely characterize the kinetic profile of LTG in this sample of patients. The k_a and V_d/F estimates obtained in the 90 patients were similar to the values obtained in previous studies [5, 21–23].

Carbamazepine, as well as phenytoin, phenobarbital and primidone, affect the glucuronidation of LTG [24]. In the present study, the fastest elimination rate constant was presented by Group 1 ($t_{½}$=10.5±4.5 h). Jawad et al. also observed similar results in nine patients taking liver enzyme-inducing AEDs [16]. The somewhat higher coefficient of variation presented by Group 1 may be attributed to the higher clearance values obtained in patients included

Table 5 Relative predictive performance of LTG serum concentrations: comparative analysis of accuracy (ME) and precision (MSE)

	Previous published sets vs. P2[a]			
Set number	1	2	3	4
ΔME[b] (μg/mL)	1.04	1.79	−0.34	2.22
	(0.46; 1.62)*	(1.19; 2.39)*	(−0.97; 0.28)	(1.61; 2.83)*
ΔMSE[b] (μg/mL)^2	−4.38	−7.20	−5.48	−8.88
	(−6.48; −2.28)*	(−10.77; −3.63)*	(−8.75; −2.20)*	(−12.83; −4.94)*

*$p \leq 0.05$
[a]P2, Parameter set established in accordance with the estimates achieved in each treatment group (Table 2). Values given are the mean (95% CI is given in parenthesis)
[b]ME, Mean prediction error; MSE, Mean squared prediction error; n=77

in the two-inducer subgroup. However, statistical analysis failed to prove any significant difference between the one- and two-inducer subgroups, probably due to the small number of patients involved in the latter. Nonetheless, vigilance should be taken when this combination is administered in order to avoid any reduction of LTG concentrations to negligible values, thereby resulting in the impairment of its antiepileptic properties. Other non-epilepsy medication may also reduce LTG levels (e.g. oral contraceptives) [25], although we found no difference between males and females with respect to kinetic behaviour.

Group 2 exhibited the longest elimination half-life (42.4±11.2 h). These results are consistent with those obtained by Yuen et al. in six volunteers [9]. The use of low-to-moderate dosages of VPA (1000 mg/day) may achieve significant increases in LTG plasma concentration [26]. In fact, the metabolism of drug seems to be inhibited at very low doses and concentrations of VPA [27]. Thus, given the high variability demonstrated by our data, it seems advisable that titration in these patients should be based on the LTG plasma concentration rather than on the crude dosage recommendations of manufacturers only. More recently, some authors have recommended the TDM of LTG in VPA co-treated patients in order to minimize the occurrence of side effects in patients with higher LTG serum levels [28].

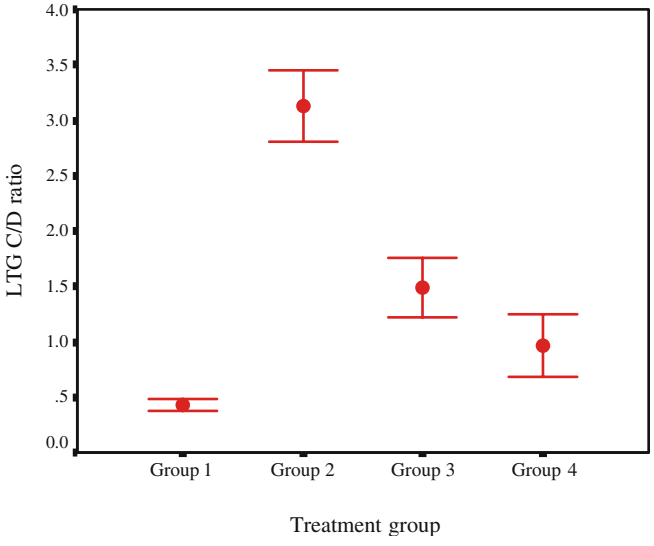

Fig. 1 Concentration-to-dose (C/D) ratio observed for the four groups established according to co-medication. Statistical differences were found between all groups ($p \leq 0.05$). *Error bars* represent the 95% CI of the means. C/D ratio, LTG concentration (mg/L) normalized by dose (mg/kg/day). Group 1, LTG+IND; Group 2, LTG+VPA; Group 3, LTG+VPA+IND; Group 4, LTG+NONE. IND, inducer; VPA,valproic acid; NONE, AEDs not known to modify drug metabolism (all data)

The estimates obtained in Group 3 ($t_{½}$=26.7±10.7 h) were found to be close to those observed in volunteers in studies by Cohen et al. [5] and by Jawad et al., in which they studied 13 patients receiving VPA together with an inducing AED [8]. These results are probably due to the capacity of both drugs to counteract the inducing/inhibitory effect, which may depend on the inducer agent involved. Phenytoin was reported to have the capacity to compensate for the inhibitory effect of VPA [16]. However, in Group 3, CBZ and FB were the main inducer agents found to be associated to LTG and VPA [CBZ (n=5); FB (n=7); PR (n=1); PHT (n=1)].

Group 4 was characterized by patients receiving neither inducers nor inhibitors of LTG metabolism – at least based on the extent of our present knowledge on the influence of the new AEDs on LTG kinetics. This group presented a lower mean half-life estimate ($t_{½}$=18.2±7.6 h) than Group 3. Interestingly, in spite of the reduced number of patients available in this group, a statistical difference between Group 3 and Group 4 was be found (Table 2). This is a relevant finding in that it may indicate that the inhibitory capacity of VPA may not be completely counteracted by the presence of the inducing agents in Group 3. In order to evaluate the potential influence of these inducers (FB/PR vs. CBZ), a t-test was performed. However, no difference could be found between these drugs in terms of their influence. In group 4, no significant difference when patients with TPM (n=3) were compared to those without TPM (n=4), although the sample size was very small. Nevertheless, clearance estimates of Group 4 are slightly higher that those obtained in patients submitted to monotherapy [29].

The validation approach allowed us to consider the ability of the established sets of PK parameters in predicting LTG concentrations, so they might be applied in clinical programmes as prior information which could be used to optimize dosage of LTG (namely, in the PKS software application for TDM). The estimation of pharmacokinetic parameters in the target population, rather than the

implementation of parameters established in other populations, improves individual estimation because it provides a more accurate and precise dosing regime design based on prior prediction. The influence of co-medication in this population was further confirmed by the use of the C/D ratio (Fig. 1). The present results are consistent with those reported in previous studies [16, 19].

The knowledge of the kinetic behaviour of the medications obtained in this medical setting (a difficult-to-treat epilepsy condition) may contribute to a better management of those patients who are submitted to VEEG monitoring for diagnostic purposes, ultimately helping to optimize the procedure to be applied in drug withdrawal protocols. This may be accomplished by using the P2 set of parameters to predict the LTG concentrations of those patients and, in addition, to allow its eventual correlation with the dynamic response.

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